REMARKS

Claims 22, 27, 39 and 40 will be pending following entry of this amendment. Claim 37 is withdrawn. Claims 23, 24, 28-32 and 60 are cancelled herein. Claims 22 is amended to specify that the amyloid fibrils are Aβ amyloid fibrils. Claim 27 is amended to specify that the disease is Alzheimer's disease. No new matter is added. Applicants reserve the right to file divisional/continuation applications to the cancelled subject matter.

THE REJECTION OF CLAIMS 22-36, 38-49, 52, 53 and 57-61 UNDER 35 U.S.C. §102(b), OVER CASTILLO *ET AL.*

Office Action maintains the rejection of claims 22-36, 38-49, 52, 53 and 57-61 under 35 U.S.C. § 102(b) as being anticipated by Castillo *et al.* (International Patent Application Publication No. WO/0012102) because the cited reference allegedly teaches using compositions in treatment of Alzheimer's disease which contain procyanidin B2 in the same concentrations as recited in the instant claims. The Office Action further alleges that the *Uncaria tomentosa* used in Castillo *et al.* contains 2% procyanidin B2 and is used in 10 to 1000 mg/kg of body weight. The Office Action cites Tuckmantel *et al.* in support of this allegation. The Office Action asserts that this amount allegedly corresponds to the amount recited in the claimed methods and compositions. The Office Action concludes that the disclosure of Castillo *et al.* allegedly inherently possess the characteristics of the claimed methods and implicitly anticipates the claims.

Applicants note that claims 23, 24, 28-32 and 60 are cancelled herein. The rejection is respectfully traversed with respect to pending claims 22, 27, 39 and 40.

Disclosure of International Patent Application Publication No. WO/0012102 by Castillo *et al.*

As discussed in the previous response, Castillo *et al.* discloses the use of a product obtained from the inner bark and/or roots from the plant *Uncaria tomentosa* in combination with one or more other ingredient listed therein in the compositions and methods for treating Alzheimer's disease amyloidosis and for improved brain cognition, memory/ recall optimization. The reference *does not disclose that the plant Uncaria tomentosa contains procyanidin B2.*

Disclosure of Tuckmantal *et al.*

The article by Tuckmantal *et al.* in *J.Am. Chem. Soc.*, 1999, 121, 12073-081, describes synthesis of procyanidin B2 from naturally occurring catechin. Applicants note that the reference *does not disclose isolation of procyanidin B2 from Uncaria tomentosa,* or any other plant for that matter. The reference describes that the compound has anti-cancer activity.

Differences between disclosure of the cited references and the instant claims

Claim 22

Independent claim 22 is directed to a method for treating the formation, deposition, accumulation, or persistence of Aβ amyloid fibrils in a mammal, by treating the fibrils with an effective amount of a procyanidin B2, wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day.

As discussed above, Castillo *et al.* discloses compositions containing the products obtained from the inner bark and/or roots from *Uncaria tomentosa* and additional blended ingredients. The reference does not disclose that the inner bark and/or roots from *Uncaria tomentosa* contain procyanidin B2. Further, Tuckmantal *et al.* describes a synthetic procedure for preparation of procyanidin B2. Thus, none of the cited references disclose presence of procyanidin B2 in *Uncaria tomentosa*, let alone presence of 2% procyanidin B2 as alleged in the Office Action. In fact, as described in the instant application *Uncaria tomentosa* contains much less procyanidin B2. As described in the application Example 10, page 45, line 30, the yield of procyanidin B2 in *Uncaria tomentosa* bark powder is about 0.05%.

Applicants are not aware of any reference that discloses presence of 2% procyanidin B2 in *Uncaria tomentosa*. There is no art of record that discloses presence of 2% procyanidin B2 in *Uncaria tomentosa*. Applicants respectfully request that if the Examiner is aware of any such reference, it be made of record.

Since the cited reference does not disclose all elements of the claimed method, the reference does not anticipate claim 22.

Claim 27

Independent claim 27 is directed to a method for treating Alzheimer's disease in a mammal by administering a therapeutically effective amount of a procyanidin B2 to the mammal wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000

mg/kg of body weight per day. Claims 39 and 40 depend from claim 27 and further define the method of claim 27.

As discussed above, neither Castillo *et al.* nor Tuckmantal *et al.* disclose that the inner bark and/or roots from *Uncaria tomentosa* contain procyanidin B2, let alone 2% procyanidin B2. Therefore, the references do not disclose treating Alzheimer's disease in a mammal with procyanidin B2 in an amount ranging from between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day as instantly claimed. Since the references do not disclose all elements of the claimed method, the references do not anticipate claim 27 or any of the dependent claims.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH: LACK OF WRITTEN DESCRIPTION

Claims 22-24, 27-32, 39, 40 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for reducing the deposition and buildup of Aβ amyloid fibrils allegedly does not provide enablement for treating Alzheimer's disease. The Office Action alleges that the specification does not enable any physician to practice the claimed subject matter. The Office Action further alleges that the main issues are the correlation between clinical efficacy for an Alzheimer's treatment and the amyloid binding assay described in the application.

Applicants respectfully request reconsideration of the rejection as it applies to pending claims 22, 27, 39 and 40 in view of the amendments and remarks herein.

Analysis

The test for enablement is whether or not any person skilled in the art could make and use the claimed subject matter from the disclosure in an application, coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988).

Applicants submit that the instant claims are directed to methods for treating the formation, deposition, accumulation, or persistence of Aβ amyloid fibrils and methods for treating Alzheimer's disease using procyanidin B2. Applicants further submit that the application defines, on page 13, lines 4-11, treatment of a disease as "treatment includes preventing the disease from occurring in a mammal that may be predisposed to the disease but

does not yet experience or exhibit symptoms of the disease (prophylactic treatment), inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease)." It is further described that "treating" amyloidosis or amyloid diseases includes any one or more of the following: preventing, inhibiting, reducing, disassembling, disrupting, and disaggregating amyloid fibrils and amyloid protein deposits, such as Aβ and the other amyloids. Therefore, the claims are limited to the treatment of specific conditions using a specific compound.

Nevertheless, the Federal Circuit has stated that with respect to the breadth of claim as it pertains to enablement, the only relevant concern should be whether the scope of enablement provided by the disclosure is commensurate with the scope of the claims. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Applicants submit that the enablement of the present disclosure is commensurate with the scope of the pending claims because the application describes how to prepare the compound used in the claimed methods and how to use the compound in the methods. The application describes formulation of the compound in suitable dosage forms and activity of the compound in an *in vitro* assay that measures inhibition/disruption of Aβ amyloid fibrils (*see,* Examples 7, 8, 13 and 14). Further data provided in the Declaration of Dr. Alan Snow (Declaration submitted with response dated February 1, 2006), demonstrates prevention of brain amyloid formation/accumulation by procyanidin B2 is APP Transgenic mice, reduction in amyloid load/plaque number in APP Transgenic Mice after treatment with procyanidin B2, reduction in amyloid load/plaque number after treatment with procyanidin B2, reduction/inhibition of brain Aβ 42/40 levels by procyanidin B2, reduction in microgliosis in APP Transgenic Mice after treatment with procyanidin B2, and *improvement in hippocampus-dependent memory (spatial acquisition) in APP Transgenic Mice* as determined by Morris Water Maze Testing.

Applicants respectfully submit that one of the characteristics of Alzheimer's disease is hippocampus-dependent memory loss. As described in the Declaration, improvement in hippocampus-dependent memory (spatial acquisition) in APP Transgenic Mice was determined by Morris Water Maze Testing. Following 90 days of i.p. injections (50 mg/kg/day) with saline (hAPPtg/saline) or procyanidin B2, APP transgenic mice and non-transgenic littermate controls

(Nontg) were tested in a Morris water maze to determine effects on hippocampus-dependent memory (spatial acquisition). Procyanidin B2 treatment demonstrated improvements in hippocampus dependent memory (by 57.8% on day 4 of the invisible platform, and by 57.3% on the 5th day of the invisible platform). This was detected by both path length (meters) and in latency (m/sec). *Procyanidin B2 treated APP* mice *had improvements in spatial acquisition approaching those levels observed in non-transgenic animals*. Further, the *in vivo* data in APP transgenic mice provided with the Declaration demonstrated reduction in amyloid load/plaque number, prevention of brain amyloid formation/accumulation, reduction/inhibition of brain Aβ 42/40 levels, reduction in microgliosis after treatment with procyanidin B.

Therefore, based on the information available in the art and the data provided by the applicant, one of skill in the art would recognize the correlation between the data provided and the clinical manifestations of Alzheimer's disease.

Applicants respectfully point out that the Federal Circuit has specifically stated that it is the Food and Drug Administration and not the PTO that determines the safety and efficacy of drugs for use in humans. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (Testing for the full safety and effectiveness ... is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings). This regulatory process is not the same as the enablement requirement under 35 U.S.C. § 112.

As demonstrated by the *in vitro* data in the application and the *in vivo* data provided in the Declaration of Dr. Alan Snow, procyanidin B2 treats formation, deposition, accumulation, or persistence of Aβ amyloid fibrils and is useful in treating Alzheimer's disease.

Rebuttal to Examiner's Arguments

1) The Office Action alleges that determining if any particular compound would treat any particular disease would require synthesis of the compound, formulation into a suitable dosage form, and testing it in an assay known to be correlated to the clinical efficacy of such treatment. The Office Action further alleges that this is large quantity of experimentation.

Applicants submit that the instant application describes how to make procyanidin B2 and how to formulate the compound in suitable dosage formats. Applicants further submit that the specification demonstrates the *in vitro* activity of procyanidin B2 in inhibition/disruption of Aβ

amyloid fibrils. The *in vivo* data was provided in the Declaration of Dr. Alan Snow to demonstrate prevention of brain amyloid formation/accumulation by procyanidin B2 in APP Transgenic Mice, reduction in amyloid load/plaque number in APP Transgenic Mice after treatment with procyanidin B2, reduction in amyloid load/plaque number after treatment with procyanidin B2, reduction/inhibition of brain Aβ 42/40 levels by procyanidin B2, reduction in microgliosis in APP Transgenic Mice after treatment with procyanidin B2 and *improvement in hippocampus-dependent memory (spatial acquisition) in APP Transgenic Mice* as determined by Morris Water Maze Testing.

Based on this information, one of skill in the art would be able to use procyanidin B2 in the instantly claimed methods without undue experimentation.

2) The Office Action alleges that the specification merely states Applicants' intention to treat Alzheimer's disease. It is further alleged that examples 7 and 14 provide no data and it is allegedly unclear if the assay described is correlated to Alzheimer's disease. The Office Action further alleges that there is no working example of treatment of any disease in man or animals. The Office Action alleged that the assay provides no evidence that the present compound affects the deposit and accumulation of amyloid fibrils. The Office Action further alleges that this does not demonstrate an Alzheimer's therapeutic effect. Applicant disagrees.

As described above, the application describes how to make procyanidin B2 and how to use it in the claimed methods. Contrary to Examiner's allegation, Examples 7 (Fig. 13) and 14 (Fig. 24) provide *in vitro* dose dependent data obtained in Thioflavin T fluorometry assay. In this assay, Thioflavin T binds specifically to fibrillar amyloid, and this binding produces a fluorescence enhancement at 485 nm that is directly proportional to the amount of amyloid fibrils formed. The higher the fluorescence, the greater the amount of amyloid fibrils formed. As described in Example 7, synthetic procyanidin B2 causes 84.5+/-7.9% disruption/disassembly of preformed Aβ 1-42 fibrils, when used at an Aβ:procyanidin B2 wt/wt ratio of 1:1, and 31.5+/-13.5% disruption when used at an Aβ:procyanidin B2 wt/wt ratio of 1:0.1. As described in Example 14, isolated procyanidin B2 causes 95.5+/-2.7% disruption/disassembly of preformed Aβ 1-42 fibrils, when used at an Aβ:procyanidin B2 wt/wt ratio of 1:1, and 61.6+/-5.8% disruption when used at an Aβ:procyanidin B2 wt/wt ratio of 1:0.1.

Examples 8 (Fig. 14) and 15 (Fig. 25) provide *in vitro* dose dependent data obtained in

Congo red binding assay. In this assay, the ability of procyanidin B2 to alter Aβ amyloid binding to Congo red is quantified. Any lowering of the Congo red color in the presence of procyanidin B2 as compared to the Congo red staining of the Aβ amyloid protein in the absence of procyanidin B2 indicates ability of procyanidin B2 to diminish/alter the amount of aggregated and congophilic Aβ amyloid. As described in Example 8, synthetic procyanidin B2 causes 46.3+/-4.3% inhibition of Congo red binding to Aβ 1-42 fibrils when used at an Aβ:procyanidin B2 wt/wt ratio of 1:1, and 30.3+/-8.0% inhibition of Congo red binding when used at an Aβ:procyanidin B2 wt/wt ratio of 1:0.1. Isolated procyanidin B2 inhibited Aβ 1-42 fibril binding to Congo red by 36.3+/-4.3% at an Aβ:procyanidin B2 wt/wt ratio of 1:1.

Further, as discussed above, *in vivo* data to demonstrate *improvement in hippocampus-dependent memory (spatial acquisition) in APP Transgenic Mice* and prevention, accumulation, reduction/inhibition of Aβ amyloid by procyanidin B2 in APP Transgenic Mice has been provided in the Declaration of Dr. Alan Snow. Applicants respectfully remind the Examiner that the Federal Circuit has specifically stated that it is the Food and Drug Administration and not the PTO that determines the safety and efficacy of drugs for use in humans.

Applicants submit that as demonstrated by the *in vitro* data in the application and the *in vivo* data provided with the Declaration of Dr. Alan Snow, procyanidin B2 treats formation, deposition, accumulation, or persistence of Aβ amyloid fibrils and *improves hippocampus-dependent memory (spatial acquisition) in APP Transgenic Mice*. Therefore, the assays described in the application provide evidence that procyanidin B2 affects the deposit and accumulation of amyloid fibrils. Furthermore, the *in vivo* data provided by the applicants demonstrates effectiveness of procyanidin B2 in treating characteristics of Alzheimer's disease, including *improvement in hippocampus-dependent memory (spatial acquisition)*.

3) The Office Action alleges that the scope of the claim involves treatment of many diseases via amyloid formation which allegedly includes hundreds of amyloid protein deposits embraced by the term amyloid. The office Action concludes that the scope of the claims is very broad.

Applicants respectfully requests reconsideration of the allegation in view of the amendments herein. The amended claims specify that the amyloid fibrils are Aβ amyloid fibrils

and the disease is Alzheimer's disease. Therefore, the scope of the claims is not broad.

Conclusion

Thus the instant specification describes the use procyanidin B2 in the methods for treating the formation, deposition, accumulation, or persistence of Aβ amyloid fibrils and methods for treating Alzheimer's disease. The working examples in the specification demonstrate the *in vitro* activity of procyanidin B2 in inhibition/disruption of Aβ amyloid fibrils. The *in vivo* data provided in the Declaration of Dr. Alan Snow demonstrates effect of procyanidin B2 treatment in prevention of brain amyloid formation/accumulation, reduction in amyloid load/plaque number, reduction in amyloid load/plaque number, reduction/inhibition of brain Aβ 42/40 levels, reduction in microgliosis and *improvement in hippocampus-dependent memory (spatial acquisition)* in APP Transgenic Mice. Therefore, in light of the scope of the claims, the description and the working examples in the application, and the high level of skill of those in this art, it would not require undue experimentation to practice the full scope of the claims. Applicant respectfully requests reconsideration and removal of the rejection.

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In view of the above, allowance of the application is respectfully requested.

Applicant hereby petitions under 37 C.F.R. §1.136 for three (3) months extension of time. Please apply the Petition for Extension of Time Fee for three months of $510 and any other charges or any credits to Jones Day Deposit Account No. 50-3013 (712576-999009).

Respectfully submitted,

Date: January 19, 2007

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